Elderly patients with multimorbidity in the home setting: umbrella review on therapeutic non-adherence causes

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Abstract. – OBJECTIVE: The elderly population is the most at risk regarding adherence, especially in the coexistence of multiple diseases. This study aims to detect factors contributing to therapeutic non-adherence in elderly patients in home settings.

MATERIALS AND METHODS: A review protocol was developed to conduct the umbrella review using the methodological framework of the Richardson et al study. The search strategy was developed in December 2022 to conduct a systematic search and to perform an Umbrella Review of systematic reviews, meta-analyses and integrative reviews published from 2012 to 2022 in English.

RESULTS: A total of 26,038 articles were identified and screened. 18 relevant articles were included in the study.

CONCLUSIONS: Therapeutic adherence in elderly patients with comorbidities in polypharmacotherapy at home is a significant problem in public health and health care. Several factors of non-adherence have been identified in the studies reviewed, confirming that the problem is multifactorial. Reducing the number of medications prescribed would appear optimal, although often not possible, as this has been seen to have an immediate positive impact. A multidisciplinary approach makes it possible not to fragment care, ensuring positive feedback on therapeutic adherence.

Key Words:
  Medication Nonadherence, Medication Noncompliance, Non-Compliance, Treatment refusal, Chronic disease, Chronic illness, Comorbidity, Pharmacotherapy.

Introduction

The coexistence of two or more chronic diseases (multimorbidity), often prevalent in the elderly population aged 65 years or older, may result in the concomitant use of multiple medications[1,2].

The elderly usually have multiple chronic comorbidities, which lead to taking numerous drugs. A condition associated with adverse drug events (ADEs), including falls, hospitalization, and death[3,4]. Moreover, polypharmacy often leads to poorer inevitably medication adherence[2]. Currently, many countries should seriously face the aging population issue1 and consider the relative consequences just reported. Although the number of drugs influences the complexity of the treatment regimen, other factors could also contribute, including dose, form, frequency of administration, and additional indications for medication use (e.g., need to take with or before food)[5]. Medication dosing involving inhalers, childproof containers, or the need to divide tablets can be challenging for the elderly. Similarly, administering multiple daily doses can lead to a lack of therapeutic adherence. These factors contributing to the treatment regimen's complexity can be critical, especially for the elderly. Similarly, administering multiple daily doses can lead to a lack of therapeutic adherence. The ability of older people to self-manage a treatment regimen is often a prerequisite for independent living at home[6], such as compliance

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with the nurse's recommendations regarding the timing, doses, and frequency of taking the medication for the entire course of therapy. Full adherence is considered only when a patient accurately follows all the physician's directions and prescriptions[7]. In the geriatric population, non-adherence has been found to result in increased hospital readmissions, length of stay, and many adverse outcomes[8-10].

The aim of this umbrella review is to detect and describe the main factors contributing to therapeutic non-adherence in elderly patients in home settings reported in the literature and contribute to identifying possible interventions needed to improve therapeutic adherence in the chronically ill elderly by ensuring good continuity of care in the home setting.

Materials and Methods

This umbrella review was conducted considering only the studies published from 2012 to 2022 and in English language.

A review protocol was developed to conduct this umbrella review using the methodological framework of Richardson et al[11].

The main research question was constructed following the PIO methodology. The revision process will be illustrated under the PRISMA methodology updated to 2020[12]. The PRISMA checklist is reported in the **Supplementary File**.

Literature Search

Through a comparison by 4 authors, the eligibility criteria, electronic databases to be used, keywords, and search strategy were determined. In this umbrella review, all studies published in English between 2012 and 2022 that involved an elderly population aged 65 years or older that self-manages chronic conditions at home were considered. Only secondary studies, such as systematic literature reviews, meta-analyses, and integrative reviews, were included. Exclusion criteria for the population were pediatric and psychiatric patients and those aged <65. Instead, primary studies and narrative reviews were excluded in relation to study types.

A search strategy was developed in December 2022 to systematically search the following databases: PUBMED, EbscoHost, and Cochrane Library. The following keywords and Boolean operators were used to find the studies of interest: (Poor Adherence OR Medication Non-adherence OR Medication Noncompliance OR Noncompliance OR Treatment Refusal) AND (Chronic Disease* OR Chronic Illness* OR Comorbidity* OR Drug Therapy OR Chronic Therapy OR Pharmacotherapy OR Polypharmacy OR Pharmacological Treatment).

Study Selection

Through the just-described search strategy, 26,038 articles were identified. After duplicate removal, achieved using Zotero® software (Vienna, Virginia, USA), 23,979 articles were screened by title and abstract according to inclusion and exclusion criteria. 77 papers were subjected to a thorough evaluation: 59 studies were eliminated after reading the full text (4 for lack of full text, 3 for study design, 18 for the target population, and 34 because they were not relevant to the research objective). Finally, the remaining 18 articles[14-31] were included because they were judged appropriately concerning the inclusion criteria.

Data Extraction and Synthesis

After reading the full texts, data and information from the 18 articles were extracted and collected and organized into a table using Excel® software. The identified review articles were distributed among the authors of this study, then two researchers independently extract data from a given article and discrepancies were resolved by consensus.

The following information was extracted from each selected review: Author, Population, Study design, Title, Year of publication, Journal, Language, and Objective of the study. Keys information reported in the reviews and meta-analyses were extracted by checking each article's results, discussion, and conclusion sections. Next, the information obtained through data extraction was compared among researchers, and all observed differences and similarities were examined. If there were any discrepancies, the input of another researcher was requested. We collected, summarized, and reported the results of this study in a descriptive way using a table (Table I).

Assessment of Quality

Using the JBI Critical Appraisal Checklist for Systematic Reviews and Research Syntheses[13], each study included was assessed for the quality of the methodology. Two reviewers participated independently, and a third reviewer was engaged only in case of disagreements (Table II).

Table I. Summary of findings.

	Authors	Population	Study Design	Title	Year	Journal	Language	Objective of the study
1	Yeam et al[28]	Patients with osteoporosis.	Systematic review.	A systematic review of factors affecting medication adherence among patients with osteoporosis.	2018	Osteoporosis. International.	E	Identify factors influencing patient adherence to anti-osteoporosis therapy.
2	Ofori-Asenso et al[31]	Patients older than 65 years taking statins.	Systematic Review and Meta-analysis.	Adherence and Persistence Among Statin Users Aged 65 Years and Over: A Systematic Review and Meta-analysis.	2018	Journals of Gerontology Series A: Biological Sciences & Medical Sciences.	E	In the present study, we sought to identify patterns of adherence and persistence among elderly people taking statins and compare adherence and persistence among users in primary and secondary prevention. This study was part of a larger review on patterns and barriers to statin use among the elderly.
3	Chen et al[21]	Patients with Acute Coronary Syndrome (ACS).	Systematic review.	Adherence to evidence-based secondary prevention pharmacotherapy in patients after an acute coronary syndrome: A systematic review.	2015	Heart & lung: the journal of critical care.	E	Assessing adherence to pharmacotherapy in secondary prevention after hospital discharge for an ACS.
4	Amha et al[29]	Epileptic patients who were taking antiepileptic drugs.	Systematic Review and Meta-analysis.	Antiseizure medication nonadherence and its associated factors among Epileptic patients in Ethiopia, a systematic review and meta-analysis.	2021	Seizure.	E	To identify the determinants of nonadherence to antiepileptic drugs (side effect, medication mechanism, availability of information, social support, perceived stigma, comorbidity, educational status, duration of treatment).
5	Dessie et al[25]	Adult patients with diabetes mellitus in Ethiopia.	Systematic and Meta-Analysis.	Association Between the Level of Reported Good Medication Adherence and the Geographic Location of a Patient's Residence and Presence of a Glucometer Among Adult Patients with Diabetes in Ethiopia: A Systematic and Meta-Analysis.	2020	Current Therapeutic Research.	E	A literature review was conducted to better understand factors associated with adherence to Diabetes Mellitus medications throughout Ethiopia and to clarify areas for further study.
6	Wimmer et al[14]	Elderly people with chronic diseases.	Systematic Review.	Clinical Outcomes Associated with Medication Regimen Complexity in Older People: A Systematic Review.	2016	Journal of the American Geriatrics Society.	E	Systematically review clinical outcomes associated with the complexity of the treatment regimen in the elderly.

Table continued

Table I *(Continued).* Summary of findings.

	Authors	Population	Study Design	Title	Year	Journal	Language	Objective of the study
7	Shariff et al[15]	Elderly people with chronic diseases aged 60 years or older.	Mixed Methods Systematic Review.	Does the Formulation of Oral Solid Dosage Forms Affect Acceptance and Adherence in Older Patients? A Mixed Methods Systematic Review.	2020	Journal of the American Medical Directors Association.	E	The purpose of this systematic review was to identify whether and how aspects of the formulation of oral solid dosage forms influence acceptance and adherence in older people.
8	Rodrigues et al[16]	Polymedicated elderly.	Integrative review.	Drug-drug interactions and adverse drug reactions in polypharmacy among older adults: an integrative review.	2016	Revista Latino-Americana de Enfermagem (RLAE).	PT/E	Identify and summarize studies examining both drug-drug interactions (DDIs) and adverse drug reactions (ADRs) in the polymedicated elderly.
9	Coleman et al[22]	Patients with cardiovascular disease.	Systematic review and Meta-analysis.	Effect of dosing frequency on chronic cardiovascular disease medication adherence.	2012	Current Medical Research & Opinion.	E	We sought to conduct a systematic review and meta-regression analysis to determine the effect of scheduled medication dosing frequency (one to four times a day) on medication adherence in chronic CVD (cardiovascular) patients.
10	Puts et al[26]	Elderly people with cancer aged 65 AA or older.	Systematic review	Factors influencing adherence to cancer treatment in older adults with cancer: a systematic review.	2014	Annals of oncology.	E	The aim of this systematic review was to synthesize all the studies to answer the research question "What factors influence adherence to active cancer treatment in the elderly aged 65 years and older diagnosed with cancer?"
11	Musawe et al[24]	Elderly patients with type 2 diabetes mellitus.	Systematic review and Meta-analyisis.	The association between polypharmacy and adverse health consequences in elderly type 2 diabetes mellitus patients; a systematic review and meta-analysis.	2019	Diabetes Res. Clinical Prac.	E	Association between polypharmacy and adverse health consequences in elderly patients with type 2 diabetes mellitus.
12	Walsh et al[17]	Patients with chronic diseases on polypharmacotherapy with age >50.	Systematic review and Meta-analyisis.	The association between medication non-adherence and adverse health outcomes in ageing populations.	2019	Br J Clin Pharmacol.	E	The purpose of this study is to synthesize the evidence on medication nonadherence and its association with health outcomes in people aged ≥50 years.
13	Yap et al[18]	Geriatric population with chronic diseases.	Systematic review.	Systematic review of the barriers affecting medication adherence in older adults.	2016	Geriatr Gerontol Int.	E	The aim of this study is to identify factors associated with medication adherence in the geriatric population.
14	Dias et al[27]	Elderly patients with oncological diseases.	Systematic review.	Refusal of medical treatment by older adults with cancer: a systematic review.	2021	APM	E	This study aims to identify predictive factors associated with treatment refusal by elderly cancer patients.

Table continued

Table I *(Continued).* Summary of findings.

Authors	Population	Study Design	Title	Year	Journal	Language	Objective of the study
15 Ozaki et al[20]	Patients on direct oral anticoagulant (DOAC) therapy in atrial fibrillation (AF).	Systematic review and Meta-analysis.	Real-World Adherence and Persistence to Direct Oral Anticoagulants in Patients With Atrial Fibrillation: A Systematic Review and Meta-Analysis.	2020	Circ Cardiovasc Qual Outcomes.	E	The purpose of this study is to assess the adherence/persistence of DOACs and evaluate the associated clinical outcomes in patients with AF.
16 Lieveld et al[30]	Elderly patients with chronic diseases and hepatitis B and C in polypharmaco-therapy.	Systematic review.	Patient adherence to antiviral treatment for chronic hepatitis B and C: a systematic review.	2015	Ann Hepatol.	E	The goal is to provide an overview of studies exploring adherence to combination treatment (PEG-interferon plus ribavirin) for HCV and nucleos(t)ide analogues for HBV.
17 Abegaz et al[23]	Elderly hypertensive patients on polypharmacotherapy.	Systematic and Meta-analysis	Nonadherence to antihypertensive drugs: A systematic review and meta-analysis.	2020	Medicine (Baltimore).	E	This systematic review applied a meta-analytic procedure to study medication nonadherence in adult hypertensive patients.
18 Maffoni et al[19]	Elderly patients with comorbidities on polypharmacotherapy.	Systematic review of qualitative studies	Medication adherence in the older adults with chronic multimorbidity: a systematic review of qualitative studies on patient's experience.	2018	Eur Geriatr Med.	E	The purpose of the study was to identify factors that influence medication adherence in older adults through a systematic review of qualitative studies on patient experience.

Legend: E= English language; PT= Portuguese language.

Table II. Quality assessment of systematic reviews included.

Authors	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Yeam et al[28] (2018)	Y	Y	Y	N	Y	Y	U	Y	N	Y	Y
Ofori-Asenso et al[31] (2018)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Chen et al[21] (2015)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Amha et al[29] (2021)	Y	Y	Y	Y	U	U	Y	Y	Y	Y	Y
Dessie et al[25] (2020)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Wimmer et al[14] (2016)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Shariff et al[15] (2020)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Rodrigues et al[16] (2016)	Y	Y	Y	N	U	Y	U	U	U	Y	Y
Coleman et al[22] (2012)	Y	Y	Y	N	U	U	U	U	U	Y	Y
Puts et al[26] (2014)	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y
Al-Musawe et al[24] (2019)	Y	Y	Y	N	U	U	U	Y	Y	Y	Y
Walsh et al[17] (2019)	Y	Y	Y	N	Y	Y	Y	U	U	Y	Y
Yap et al[18] (2016)	Y	Y	Y	N	U	U	U	U	U	Y	Y
Dias et al[27] (2021)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Ozaki et al[20] (2020)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Lieveld, et al[30] (2015)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Abegaz et al[23] (2020)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Maffoni et al[19] (2018)	Y	Y	Y	N	U	Y	Y	U	U	U	Y

Legend: Y= yes; U= uncertain; N= no. Q1: Is the review question clearly and explicitly stated? Q2: Were the inclusion criteria appropriate for the review question? Q3: Was the search strategy appropriate? Q4: Were the sources and resources used to search for studies adequate? Q5: Were the criteria for appraising studies appropriate? Q6: Was critical appraisal conducted by two or more reviewers independently? Q7: Were the methods to minimize errors in data extraction? Q8: Were the methods used to combine studies appropriate? Q9: Was the likelihood of publication bias assessed? Q10: Were recommendations for policy and/ or practice supported by the reported data? Q11: Were the specific directives for new research appropriate?

Results

Study Selection

In this umbrella review, 18 records pertaining to the research question were included. After retrieving the full texts, each study was carefully analyzed, reporting the data of interest in specific tables and dividing the records based on common characteristics. Figure 1 shows the search and selection process according to the PRISMA statement[12].

Characteristics of Included Studies

The main characteristics of the selected reviews are reported in Table I. The 18 reviews included 8 meta-analyses[14,16,17,21,23,24,27,29]. 6 studies[14-19] have elderly patients with multiple chronic diseases as their focus population, 5 articles[20-23] focused on cardiovascular diseases, 2 articles[24-25] focused the analysis on patients with diabetes mellitus, 2 articles[26,27] concerned patients with cancer, 1 paper[28] analyzed patients with osteoporosis, 1 study[29] investigated patients with epilepsy, and one article[30] studied patients with viral hepatitis B and C. Three of these reviews[16,26,28] identified and classified factors associated with non-adherence into five categories and related subcategories. All studies have involved patients with chronic diseases undergoing drug treatment self-managed at home.

Findings of the Review

In this research work, most of the studies[14,19-30] are characterized by a target population of elderly patients with chronic diseases.

The article by Wimmer et al[14] systematically reviews clinical outcomes associated with treatment regimen complexity in the elderly. In their review, evidence from four studies suggests that drug regimen complexity is associated with non-adherence and higher hospitalization rates[14]. Instead, the study by Shariff et al[15] investigated whether and how the characteristics of oral solid dosage forms affect acceptance and adherence in older people. Too large a tablet size is the most common cause of swallowing difficulties, but, at the same time, tablets that are too small result difficult to handle.

On the other hand, regarding the drug's outward appearance, it has been seen that patients have difficulty distinguishing between different dosages due to similarities in appearance, resulting in discomfort and clinical deterioration.

The work of Rodrigues and Oliveira[16] identified that healthcare providers' early diagnosis and recognition of drug interactions and clinically significant adverse drug reactions are vital to identifying patients at higher risk of such events
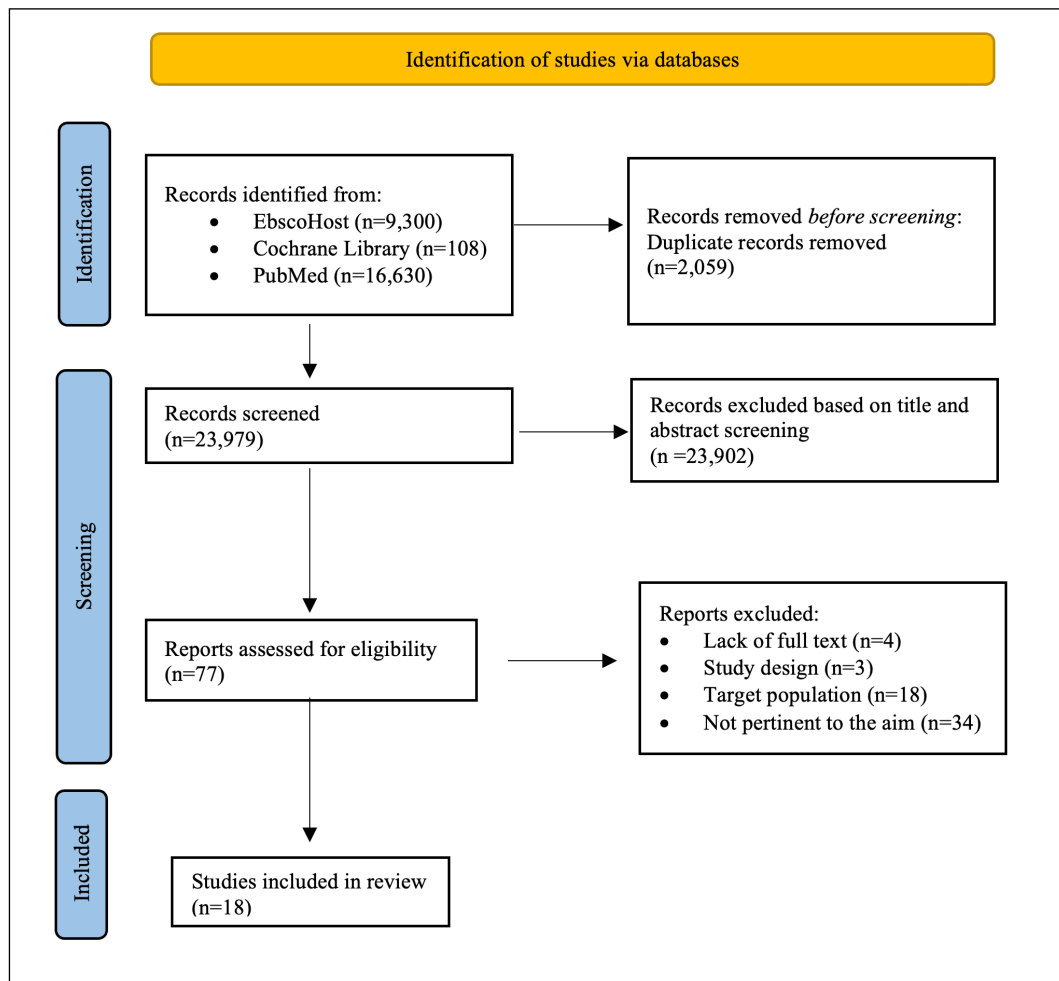
Figure 1. Flow diagram of the search and selection process, based on the PRISMA flowchart.

and requiring more careful drug-therapeutic management to avoid adverse outcomes.

The study by Walsh et al[17] showed that nonadherent individuals had a 17% higher risk of hospitalization (for any cause).

Yap et al[18], considering the adverse health events of the elderly nonadherent to therapy, conducted a major study to identify and classify factors influencing adherence and proposed a flower model to facilitate the understanding of the complex nature of adherence and to optimize treatment outcomes.

In contrast, the record by Lieveld et al[30] focused on the problems of treatment non-adherence in patients with chronic hepatitis B and C disease. Studies reported the highest adherence rates when were used patients' self-report assessments.

Finally, Maffoni et al[19] identified factors influencing medication adherence in the elderly through a systematic review of qualitative studies focused on patient experience from Western cultures and

societies. It was found that non-perception of physical symptoms often leads to non-treatment, medication refusal or non-adherence.

Of the 18 articles, five[20-23,31] focused on elderly patients with cardiovascular disease. The study by Ofori-Asenso et al[31] aimed to identify and compare adherence and persistence patterns among the elderly in primary and secondary prevention. According to this analysis, nearly one in four patients who had just initiated statin therapy discontinued the drug within the first 12 months of treatment. The reasons for these interruptions in taking the prescribed medication are caused by the lack of effectiveness of the drug or the occurrence of adverse effects, especially since aging may result in altered pharmacokinetics and pharmacodynamics of the drug.

Chen et al[21] review evaluates adherence to pharmacotherapy in secondary prevention in adult patients after hospital discharge for acute coronary

syndrome (ACS). The economic aspect has been shown to affect medication adherence significantly.

The article by Coleman et al[22] also reveals that patients with chronic cardiovascular disease adhere more to once-daily drug regimens than those given more frequently.

Ozaki et al[20] investigated the adherence to direct oral anticoagulant drugs [(DOACs) known as new oral anticoagulants (NAOs)], in patients with atrial fibrillation (AF). Their study analyses adherence to various DOAC medications by showing that it can be influenced by side effects such as gastrointestinal discomfort and cost-effectiveness.

Abegaz et al[23] have studied medication non-adherence in patients with hypertension. A significant number of nonadherent hypertensive patients were identified at 45.2%. In addition, the association between hypertension and multiple diseases showed a non-adherence of 31.2%. Although a higher percentage (54%) of non-adherence to antihypertensive medications was observed in females, the risk of non-adherence was 1.3 times higher in males. In addition, African (62.4%) and Asian (43.5%) individuals showed lower adherence than other ethnicities.

Two other articles[24,25] highlighted therapeutic adherence in patients with diabetes. Dessie et al[25] conducted a systematic review to understand better the factors associated with therapeutic adherence of individuals with diabetes mellitus in Ethiopia. This study showed that 68.59% of patients with diabetes in Ethiopia had good medication adherence. Good adherence levels improved when patients had access to a glucose meter to monitor glucose levels independently, regardless of the region in which they lived. However, socioeconomic factors (patients with high income and higher education) may ensure greater availability of glucometers and, consequently, greater adherence.

The work of Labib Al-Musawe and colleagues[24] summarizes the existing literature on the association between polypharmacotherapy and adverse health consequences in elderly patients with type 2 diabetes mellitus. Unfortunately, increased therapy may increase the risk of adverse health outcomes.

Two papers[26,27] have investigated treatment adherence in oncological patients. The research conducted by Puts et al[26] has focused on adherence to all active cancer treatments in the elderly diagnosed with cancer. Non-adherence was found to be common, but little is known about the non-adherence influencing factors in this population, especially for cancer treatments *vs.* other hormonal therapies among elderly men. The literature review

by Dias et al[27] identified factors predictive of treatment refusal in patients with neoplastic disease. These include age, female sex, celibacy, non-white race, public insurance availability, socioeconomic status, stage of disease, and comorbidity.

The study by Amha et al[29] on epileptic patients taking antiepileptic drugs aimed to identify some determinants of non-adherence to pharmacotherapy. The cost of drugs, duration of therapy, comorbidity, and perceived stigma were all significant factors influencing adherence.

Specifically, three of the studies[18,19,26] already mentioned, identified and classified some factors associated with non-adherence into categories and subcategories. In the paper by Yeam et al[28], whose study population was patients with osteoporosis, a total of 24 factors with 139 subfactors were identified and classified based on the five dimensions of adherence suggested by WHO[32]. Among factors related to the condition, the concomitant administration of more medications for comorbidities was associated with lower medication adherence[19]. In addition, psychiatric disorders such as depression are associated with poorer medication adherence among patients with osteoporosis[28]. Patient-related factors associated with lower medication adherence included older age and misconceptions about osteoporosis, while therapy-related factors included higher dosing frequency and medication side effects[26]. Health system-based factors associated with lower medication adherence included care in different medical specialties and lack of patient education. Socioeconomic factors associated with lower medication adherence included smoking and lack of medical insurance coverage[28].

In the study of Maffoni et al[19], several barriers and facilitators of non-adherence have emerged from patients' narratives, which were grouped into the following areas: patient beliefs and concerns about treatment, patient beliefs about polypharmacotherapy, patient experience and skills, physician-patient relationship, health literacy, characteristics and complexity of treatment, family and social support.

The study by Yap et al[18] summarized the literature as much as possible and briefly presented the various factors in five main categories to enable health professionals to understand better the complex nature of therapeutic adherence in older people.

Quality Assessment

The quality of the methodology for each systematic review included in this study was assessed

under the JBI Critical Appraisal Checklist for Systematic Reviews and Research Syntheses[33]. None of the reviews in this umbrella were excluded based on this methodological quality criteria. In 14 selected studies[15-22,25,27,28,30], a comprehensive search strategy was not demonstrated; of these, only one article[28] stated that the likelihood of publication bias had not been assessed (criterion 4 and 9). Regarding the quality, 9 out of 18[14,15,20,21,23,25,27,30,31] reviews included in the study can be classified as strong, while five reviews are moderate.

Discussion

The main objective of this umbrella review is to identify the critical factors associated with non-adherence to therapeutic treatments in elderly patients with chronic diseases. In the included reviews, different causes of non-adherence were identified, summarized, and finally reported in Table III. Although the reviewed studies considered a wide range of chronic diseases, most were focused on cardiovascular diseases. Of the 18 reviews considered, all identified at least one predictor of non-adherence, and all but seven[14,15,17-19,26,27] reported rates of adherence or non-adherence in therapeutic regimes.

Specifically, in four articles[18,19,26,28], after identifying all factors associated with non-adherence, they classified them as categories and subcategories. The WHO has described five groups of factors that influence treatment adherence, and in this umbrella review, we found evidence to support each of these groups of factors influencing adherence in this population.

Drug non-adherence is a complex and multifactorial phenomenon. Several studies[26-28] have demonstrated the association between non-adherence and comorbidity, polypharmacotherapy, therapeutic regimen complexity, and socioeconomic status. In the elderly population over 65, comorbidity affects costs and drug treatment adherence because it generally involves taking more medications[14]. In 2018, in several European populations it was found that 32.1% of patients aged 65 years and older take more than five or more medications[34].

It is recommended to consider deprescribing drug therapy after reviewing a patient's medication list, when safe and possible. It has been found that simplifying the treatment regimen with less frequent daily dosing appears to be a reasonable intervention[22,24].

The factors associated with non-adherence are not all consistent in the studies analyzed. For example, the study of Ozaki[20], which examines the adherence to various oral anticoagulant drugs in patients with atrial fibrillation (AF), argues that the dosing regimen of two or once daily has an insignificant impact on adherence while significantly affecting treatment adherence, side effects like gastrointestinal discomfort and cost-effectiveness.

In contrast, a 2009 study[35] showed that adult patients at high cardiovascular risk who correctly adhere to ACE inhibitor therapy every day, regardless of dosage, have significantly increased serum concentrations of insulin-like growth factor (IGF-1) and insulin-like growth factor-3 binding protein (IGFBP-3) in the blood. Also, in the paper of Osasu et al[36], factors such as age, multimorbidity, and polypharmacotherapy influence physicians prescribing of anticoagulant drugs due to the increased bleeding risk. In addition, a lack of physician/patient trust and poor understanding influence therapeutic nonadherence[37]. In the study by Amha et al[29] conducted in Ethiopia, a significant association was shown between medication costs and non-adherence. Epilepsy patients who received paid medications were 3.7 times more likely to be nonadherent than patients who received free drugs. Healthcare providers can help low-income patients identify programs that improve access to effective medicines for these patients[21]. In an Ethiopian study, Dessie et al[25] found that patients with diabetes mellitus were more adherent to therapeutic treatment when possessing a glucometer. This is probably because a glucometer allows patients to measure their blood glucose regularly and prevent hyperglycemia or hypoglycemia. A reduced level of education and low socioeconomic status are both considered significant variables in treatment refusal[27]. Moreover, ethnicity could be a relevant factor related to lower adherence rates or more substantial exposure to chronic diseases. For example, African Americans are more exposed to hypertension than others. Female sex is also associated with therapeutic non-adherence, as demonstrated in studies by Dias et al[27] and Abegaz et al[23].

Patients with misconceptions about their disease and failure to perceive treatment benefits have been associated with lower medication adherence due to the lack of patient support and education from healthcare providers[26,28]. There is evidence that adherence increases with a more excellent perception of the life-threatening risk[19,31]. Confirming this, Kronish et al[38] reported that 38%

Table III. Factors associated with nonadherence.

Author	Pathologies	Factors associated with nonadherence	Adherence/non-adherence rate
Yeam et al[28] (2018)	Osteoporosis	Past medical history, comorbidities, screening, demographic characteristics, physical and mental functions, menopause-related factors, perceptions about the disease and treatment, family history, drug dosing regimens, drug side effects, types of osteoporosis drugs, other drug-related factors, past history of osteoporotic drugs, health care provider-related factors, health care facility-related factors, socioeconomic factors, lifestyle factors.	Therapeutic adherence from 12.9% to 95.4%.
Ofori-Asenso et al[31] (2018)	Cardiovascular disease.	Poor drug efficacy, adverse effects, perceived low risk, polypharmacotherapy, cognitive decline, and other barriers (e.g., difficulty swallowing).	Adherence at 1 year of treatment 59.7%.
Chen et al[21] (2015)	Acute coronary syndrome (ACS).	Costs, side effects, frequency in daily medication intake, poor universal health care.	Therapeutic adherence from 54% to 86% in patients discharged from hospital after SCA.
Amha et al[29] (2021)	Epilepsy	Cost of medication, duration of therapy, perceived stigma, comorbidity.	Therapeutic adherence of 58%.
Dessie et al[25] (2020)	Diabetes	Comorbidity, cost of medications, accessibility of health care facilities, lack of patient education, and poor patient-caregiver relationship.	Therapeutic adherence of 68.59%.
Wimmer et al[14] (2016)	Chronic diseases	Complexity of treatment regimen, nonefficacy of drugs.	
Shariff et al[15] (2020)	Chronic diseases	Appetizability, outward appearance, size of oral therapy.	
Rodrigues et al[26] (2016)	Chronic diseases	Drug-drug interactions (DDIs) and adverse drug reactions (ADRs) related to polypharmacotherapy, alcohol consumption and 'smoking habit, age, and comorbidities.	
Coleman et al[22] (2012)	Cardiovascular disease	Complexity of cardiovascular drug regimen (multiple daily administrations).	Adherence to taking medication once a day is 79%.
Puts et al[26] (2014)	Oncological pathologies	Older age, nonwhite race, celibacy, dementia, denial of cancer diagnosis, psychiatric illness, alcohol dependence, difficulty understanding treatment indications or having forgotten treatment, number of hospitalizations, cancer recurrence, negative or neutral beliefs about the value of treatment treatment-related side effects, use of antidepressants at the time of initiation of, polypharmacotherapy, follow-up appointments and drug prescriptions provided by a primary care physician instead of an oncologist, long waiting times at outpatient clinics and having to travel long distances to get to clinics, economic reasons.	Therapeutic adherence from 52% to 100%.
Al-Musawe et al[24] (2019)	Diabetes	Polypharmacotherapy	Nonadherence to hypoglycemic drugs ranges from 53% to 65% at 1 year.

Table continued

Table III *(Continued).* Factors associated with nonadherence.

Author	Pathologies	Factors associated with nonadherence	Adherence/non-adherence rate
Walsh et al[17] (2019)	Chronic diseases	Drug-related factors such as dosage regimen, side effects, polypharmacotherapy, patient-related factors such as cognitive function and age, health literacy, multimorbidity.	
Yap et al[18] (2016)	Chronic diseases	Mental status, physical health, demographics, disease history, patient knowledge or beliefs, medication regimen, medication intake, poor communication, lack of patient involvement, lack of trust in physician professionalism, prescribing by nonspecialists, dissatisfaction with doctor's visits, lack of patient education, lack of follow-up, lack of treatment plan, duration of treatment, lack of community nursing services, lack of caregivers, lack of immediate improvement in health status.	
Dias et al[27] (2021)	Oncological pathologies	Female gender, celibacy, nonwhite race, non-public insurance possession, socioeconomic status, poor education, the stage of illness, poor health status, advanced age.	
Ozaki et al[20] (2020)	Atrial fibrillation	Gastrointestinal problems, cost-effectiveness.	Average cumulative adherence at 1 year is 80%.
Lieveld et al[30] (2015)	Hepatitis B and C	Nonadherence to treatment in chronic viral hepatitis is not a frequent phenomenon. The lowest adherence rates were reported in studies using pharmacy claims.	For HCV, the average adherence ranges from 27% to 97%. Average adherence reported in HBV studies ranges from 81% to 99%.
Abegaz et al[23] (2018)	Hypertensive patients	Comorbidity, socioeconomic status, health literacy, race/ethnicity, female gender.	Nonadherence to hypertension is 45%. Hypertension and multiple diseases showed a nonadherence of 31.2%.
Maffoni et al[19] (2018)	Chronic diseases	Nonperception of physical symptoms, lower perception of risk to life, ethnicity (African American), socioeconomic status.	

of the surveyed sample became more adherent to their drug therapy after hospitalization for acute myocardial infarction among elderly patients who had not taken statins. The use of antidepressants is common in elderly patients with multiple diseases. In the study by Yeam et al[28], it was reported that depressed patients are twice as likely to be nonadherent to their chronic disease medications than patients without depression.

Conclusions

This study aimed to collect therapeutic non-adherence causes in patients over 65 years old with comorbidities in the home context. Identifying and knowing all factors contributing to poor adherence to the treatment plan allows the foundation to be laid for improved care and care pathways in a setting other than the hospital setting. Analysis of the literature has suggested how the presence of comorbidities leads to increased medications and therapeutic non-adherence, so just the simple reduction of drugs could have positive and rapid results. It is also pointed out that using a technique of active participation by the patient during prescribing dramatically reduces non-adherence. To be counted among the possible variables to enhance therapeutic adherence in the elderly with comorbidity is to foster an adequate socioeconomic situation.

The strengths of this review can be identified in the systematic methodology used to identify all relevant articles using two independent reviewers, including multiple databases and a search string that allowed many records to be identified.

Our review has some limitations. First, following the umbrella review methodology, we extracted evidence from the secondary literature rather than the primary articles. Therefore, we did not evaluate every aspect of the source of the original article to draw direct conclusions. Similarly, the heterogeneity of the included studies in assessment methods, study populations, and outcomes made it challenging to identify non-adherence factors associated with and consistent with all studies.

Future research must address the problem of multiple drug prescribing and develop methods of pharmaco-epidemiology in comorbidity. As seen from the articles reviewed, a multidisciplinary approach is needed to avoid fragmenting care and thus ensure positive feedback on treatment adherence.

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